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PHENYTOIN DOSE ADJUSTMENT IN EPILEPTIC PATIENTS

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1 A preliminary survey showed that many outpatients with partially controlled epilepsy had serum concentrations of phenytoin below the recommended therapeutic range (10-20 μg/ml). A phenytoin tolerance test was devised with the intention of predicting a more adequate daily dose for such a patient.

2 Fifteen patients were each given an oral test dose of 600 mg phenytoin sodium and the serum concentration of phenytoin was measured at intervals over 48 h; the concentration rose during the first 4 h and decayed between 12-48 h as an almost linear function of time.

3 The serum concentration/time curves were fitted by an iterative computer program based on the Michaelis-Menten equation. The mean saturated rate of elimination of phenytoin was 435 mg/day and the serum concentration (K_m) corresponding with 50% saturation was 3.8 μg/ml. The mean calculated dose of phenytoin sodium required for a steady state serum concentration of 10-20 μg/ml was 345-400 mg/day.

4 The Michaelis-Menten principle was used to predict steady state serum phenytoin concentrations in individual patients receiving daily doses of phenytoin sodium adjusted by steps of 100 mg. The serum concentrations tended to be either too low or too high. The steep relationship between phenytoin concentration and dose indicates that when the concentration reaches 5-10 μg/ml it is then appropriate to adjust dose by small steps of about 25 mg.

Introduction

Epileptic patients probably show the best therapeutic response to phenytoin when the serum concentration is between 10 and 20 μg/ml (Kutt & McDowell, 1968). Higher serum concentrations produce dysarthria, nystagmus and ataxia whereas lower concentrations probably do not allow the drug to produce its maximum anticonvulsant effect. A preliminary survey showed that many patients with partially controlled epilepsy had serum phenytoin concentrations below 10 μg/ml. This paper describes a method for estimating the daily dose required by an individual patient to produce a steady state serum phenytoin concentration within the recommended therapeutic range. Evidence will be presented to show that the elimination of phenytoin is a saturable phenomenon and that the daily dose requirement is therefore very critical.

Methods

Outpatient survey

Epileptic patients receiving phenytoin who attended the Neurology outpatient clinic of the Manchester Royal Infirmary were interviewed and examined. The type of epilepsy, the frequency of the attacks, the physical signs of drug toxicity and the doses of the drugs taken were recorded. Samples of venous blood were taken for the measurement of serum phenytoin concentration.

Phenytoin tolerance test

Fifteen outpatients with epilepsy which was only partially controlled were admitted to the Programmed Investigation Unit of the Manchester Royal Infirmary. The last regular dose of phenytoin was taken at 22.00 h on the day before the

phenytoin tolerance test. Other drugs (Table 1) were given at the usual dosage during the test.

At 10.00 h on the first day of the test a venous blood sample was taken and six 100 mg tablets of phenytoin sodium BP (Boots, Nottingham) were given by mouth. No further phenytoin was given for the next 48 h but venous blood samples were taken at 1, 2, 4, 12, 24, 36 and 48 hours.

After completion of the test, phenytoin sodium was prescribed in a regular daily dose which was adjusted later when the results of the tolerance test had been analysed.

Despite the large test dose no evidence of acute phenytoin toxicity was detected and despite the long period without phenytoin administration only two patients suffered a grand mal fit during the test. The patients clearly understood that the studies were partly experimental but that the purpose was to determine the optimum daily dose of phenytoin for each individual.

Analysis of serum samples

Each blood sample was divided into two aliquots for independent analysis by different methods in separate laboratories. One aliquot was analysed by chloroform extraction and alkaline permanganate oxidation to benzophenone (Wallace, 1968). The other aliquot was buffered to pH 6.5 and extracted with diethylether. The phenytoin and internal standard (5-methylphenyl-5-phenylhydantoin) were measured directly in the concentrated extract by gas-liquid chromatography on Gas-chrom Q coated with 3% (w/w) OV 17 using temperature programming from 180°C to 280°C at 8°/minute. The chromatograph was a Pye 104 series, with dual flame ionization detectors.

There was no significant difference between the mean concentration measured by permanganate oxidation (10.62 μg/ml) and that measured by gas-liquid chromatography (10.60 μg/ml; paired t test, $t = 0.04$, $P = 0.48$, n = 137). For each sample the average of the two measurements was taken as the best estimate of phenytoin concentration.

Curve fitting

The concentration/time curves obtained from the patients who received the test dose were fitted by an iterative computer program executed on a Nova computer (Data General Corporation, Southboro, Massachusetts). It was assumed that phenytoin was completely absorbed from the gut at a rate defined by an exponential rate constant K_a (h^{-1}), that the drug was then distributed in a single body compartment of volume V_d (litres) and that the serum concentration C_t (μg/ml) decayed in accordance with the Michaelis-Menten equation (1) (Gerber & Wagner, 1972).

$$(1) \quad \frac{dC_t}{dt} = \frac{V_{max} \cdot C_t}{(K_m + C_t)} \ (\mu g/ml)/day$$

V_{max} (μg/ml)/day represents the decay of serum concentration when elimination is saturated and K_m (μg/ml) the serum concentration giving 50% saturation.

The computer adjusted K_a, V_d, V_{max} and K_m until a least squares fit was obtained between a theoretical concentration/time curve and the experimental values. A similar method has been used independently by Atkinson & Shaw (1973).

The maintenance doses Q_{10} and Q_{20} of phenytoin sodium corresponding with steady state serum phenytoin concentrations C of 10 and 20 μg/ml were calculated by substitution into equation 2.

Under steady state conditions the rate of administration of phenytoin, $0.92\,Q$ mg/day, is equal to the rate of phenytoin elimination, $V_d \cdot dC/dt$. From equation (1) it follows that

$$(2) \quad Q = \frac{V_d \cdot V_{max} \cdot C}{0.92(K_m + C)}$$

The usual practice of prescribing daily doses in multiples of 100 mg phenytoin sodium was followed although during the study it became clear that this increment was too large. Blood samples for the estimation of the steady state serum phenytoin concentration were obtained from patients who had been receiving the same maintenance dose for several weeks. The samples were taken on attendance at the outpatient clinic and did not bear a fixed relationship to the time of the previous dose of phenytoin. Variation from this source was negligible by comparison with variation due to progressive accumulation or elimination extending over several weeks (Figure 5).

Results

Fifty outpatients receiving phenytoin therapy were interviewed. Thirty-five had serum phenytoin concentrations below 10 μg/ml. The relationship between the frequency of fits and the serum phenytoin concentration in patients with grand mal epilepsy is shown in Figure 1. A similar relationship was seen in patients with psychomotor epilepsy.

The mean result of the phenytoin tolerance test in 10 patients is shown in Figure 2. The decay of concentration between 12 and 48 h was almost linear. The results of the tolerance test in 15 individual patients are summarized in Table 1. The theoretical daily doses (Q_{10} and Q_{20}) of phenytoin

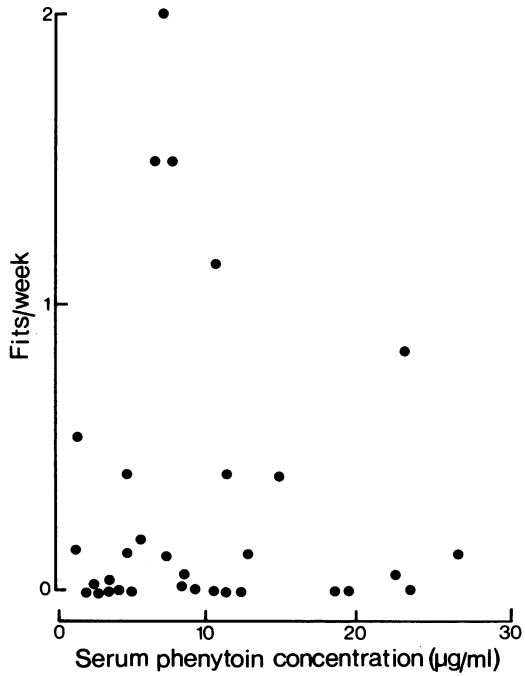

Fig. 1 Relationship between the frequency of grand mal attacks and the serum phenytoin concentration. Many patients with incomplete control of epilepsy had serum phenytoin concentrations below the lower limit of the recommended therapeutic range (10 μg/ml).

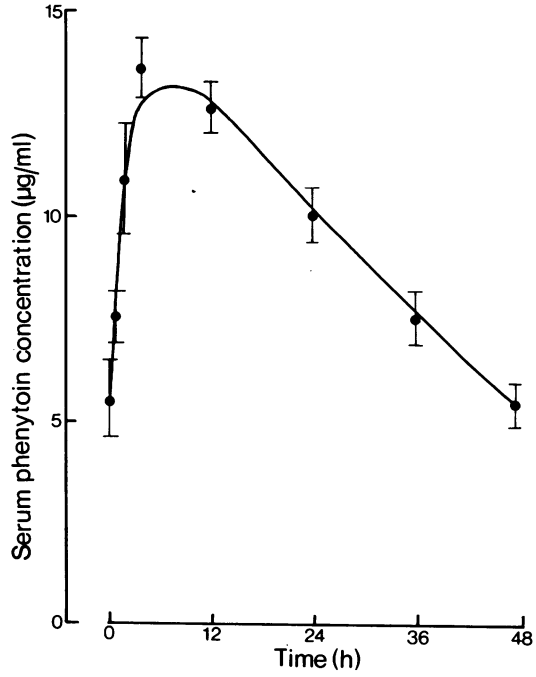

Fig. 2 Phenytoin tolerance test; serum concentrations of phenytoin (mean ± s.e. mean) in 10 epileptic patients during the first 48 h after a single oral dose of 600 mg phenytoin sodium BP. Regular phenytoin dosage was stopped 12 h before the test dose. The curve was fitted by an iterative computer program which estimated the absorption rate constant K_a as 0.4 (h^{-1}), the distribution volume V_d as 53 (litres), the maximum rate of phenytoin (acid) elimination as 410 (mg/day) and the effective Michaelis-Menten constant K_m as 4.1 (μg/ml). The almost linear decay was consistent with a saturable elimination process. Five patients were not included in this curve because serum samples had not been obtained during the first 4 hours.

sodium for steady state serum concentrations of 10 μg/ml and 20 μg/ml were calculated. When the daily dose prescribed lay outside these limits a steady state concentration below 10 μg/ml or above 20 μg/ml was predicted. The prediction was correct on 15 occasions out of 18 (Figure 3).

The theoretical curve relating steady state serum concentration to daily dose, derived from the mean results of the phenytoin tolerance tests, is shown in Figure 4. The curve rises steeply above 10 μg/ml.

The steepness of the curve was well illustrated by a female patient with grand mal epilepsy who was a shorthand typist. Serum concentrations of 7.6 and 4.2 μg/ml were observed on two consecutive visits whilst she was taking 300 mg sodium phenytoin daily. Between the two visits she had a major convulsion. The maintenance dose was accordingly increased to 350 mg daily and 35 days later she returned complaining of incoordination and an unacceptable frequency of typing errors. Her serum phenytoin concentration had risen to 27 μg/ml.

Relatively large changes in concentration for small changes in dose were also recorded in another patient (Figure 5).

Discussion

The relationship between the daily dose of phenytoin sodium and the steady state serum concentration is not linear. Bochner, Hooper, Tyrer & Eadie (1972) showed that when the serum concentration was less than 6-9 μg/ml, dose increments of 100 mg produced only small increments in concentration but when the concentration was already above this range the same dose increment produced a disproportionately large increase in

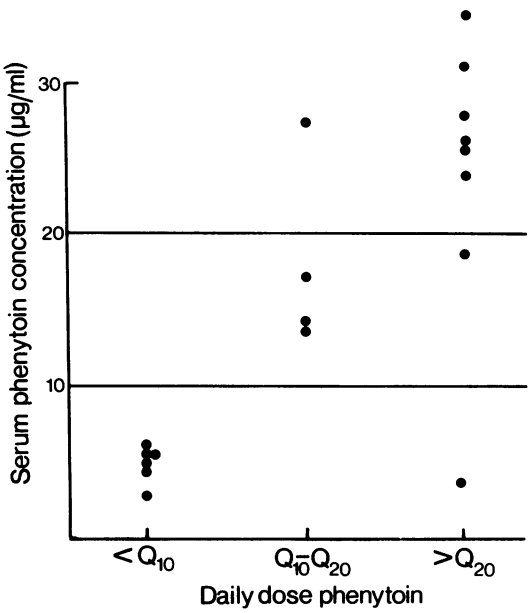

Fig. 3 Serum concentrations of phenytoin measured during maintenance treatment of the outpatients listed in Table 1. Daily doses were prescribed in multiples of 100 mg. When this dose was below the calculated dose for a concentration of 10 μg/ml ($<Q_{10}$), the measured concentration was invariably below 10 μg/ml. When the dose exceeded Q_{20} the serum concentration usually exceeded 20 μg/ml. The use of 100 mg dose increments resulted in few patients receiving a daily dose between Q_{10} and Q_{20}. Follow up samples were not obtained from three patients and several contributed more than one point to the graph.

concentration. In one patient the serum concentration rose from 12 to 26 μg/ml in response to a dose increment of only 30 mg. This type of relationship is predictable (Fig. 4) if it is accepted that phenytoin disposition conforms to Michaelis-Menten kinetics (Gerber & Wagner, 1972; Atkinson & Shaw, 1973).

The disposition of phenytoin in an individual patient has been described in terms of four parameters (Figure 2). Absorption was rapid relative to elimination and individual differences in absorption rate constant were probably not important. The effective distribution volume was positively correlated with body weight ($r = 0.75$, $P < 0.005$) and the mean value of 0.89 ± 0.07 (litres/kg ± s.e. mean) was similar to the estimates obtained by other workers (Glazko, Chang, Baukema, Dill, Goulet & Buchanan, 1969; Atkinson & Shaw, 1973). Estimates of the Michaelis-Menten constant (K_m) varied between individuals

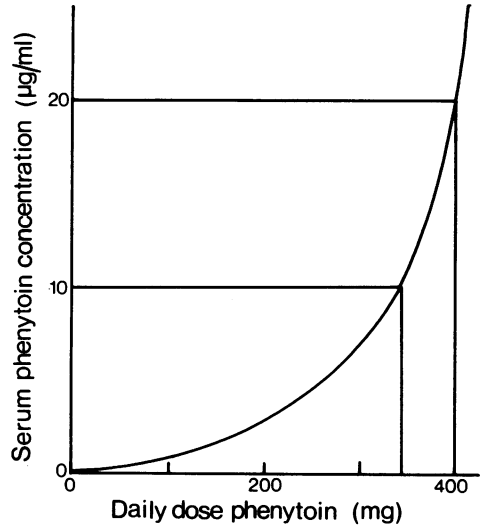

Fig. 4 Theoretical relationship between steady state serum phenytoin concentration C μg/ml) and daily dose of phenytoin sodium (Q mg/day). The curve was calculated from equation (2) by substituting the mean values for K_m and (V_d. V_{max}) given in Table 1.

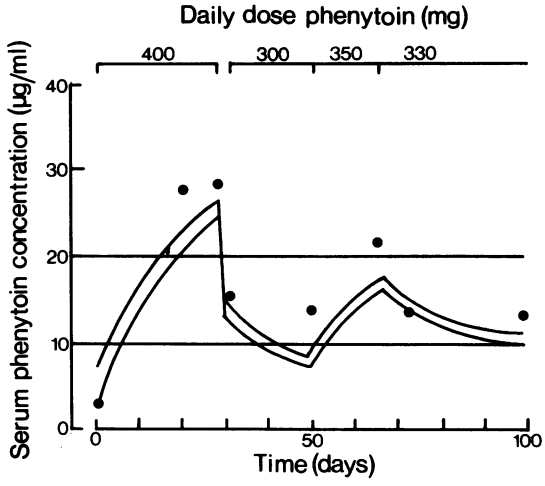

Fig. 5 Phenytoin dose adjustment in patient 5 (Table 1). The points represent measured concentrations; the continuous lines represent the range of peak and trough concentration predicted by the mathematical model using the Michaelis-Menten parameters obtained from his earlier phenytoin tolerance test. The analysis of the test slightly over estimated the rate of phenytoin elimination but the general agreement demonstrated that the model had predictive value.

Table 1 Results of phenytoin tolerance tests in individual patients

Sex	Age (years)	Body weight (kg)	Type of epilepsy	Other anticonvulsant drugs (mg/day)				K_m* (μg/ml)	Distribution volume (V_d)* (litres)	V_{max}* (μg/ml)/day	Saturated** elimination rate $V_d.V_{max}$ (mg/day)	Calculated maintenance doses (mg/day)	
				Ph	Pr	D	E					Q_{10}†	Q_{20}†
M	17	58	grand mal		750			5.8	46	6.0	275	190	230
M	37	68	grand mal	150				1.5	53	5.9	310	295	315
F	22	60	grand mal	180		15		4.0	41	7.7	315	245	285
M	26	80	grand mal	60				3.1	96	3.8	365	300	345
M	31	70	psychomotor	180		15		2.8	60	6.5	390	330	370
F	31	53	grand mal		250			4.4	45	9.0	405	305	360
M	30	77	grand mal	240	500			4.5	67	6.5	430	325	380
M	17	53	myoclonic					2.9	64	6.8	430	365	410
F	48	51	grand mal		750			5.0	35	13.2	460	335	400
F	27	60	grand mal					4.0	39	11.8	460	355	415
F	40	105	grand mal					2.7	155	3.3	510	440	490
M	22	75	grand mal	120			500	3.9	92	5.6	515	405	470
M	51	85	grand mal					3.8	42	12.6	530	420	485
M	34	85	grand mal	60	1000			3.5	60	9.0	540	435	500
M	37	60	psychomotor	90				4.6	50	11.6	585	435	515
mean	31	69						3.8	63	8.0	435	345	400
±s.e. mean	3	4						0.3	8	0.8	24	19	22

* Computer fitted Michaelis-Menten parameters.
** Rounded off to the nearest 5 mg/day.
† Theoretical doses of phenytoin sodium for steady state serum concentrations of 10 and 20 μg/ml.
Ph, phenobarbitone; Pr, primidone; D, diazepam; E, ethosuximide.

over a four-fold range (Table 1). The highest value was similar to that of Gerber & Wagner (1972) but smaller than that of Atkinson & Shaw (1973). The estimates of V_{max} varied over a two-fold range which included the values obtained by the above authors. When estimates of V_d, K_m and V_{max} had been obtained for an individual patient it was possible to calculate a range of maintenance doses which would give a serum concentration of 10-20 μg/ml (Table 1).

If the calculated maintenance doses in Table 1 are correct and the physician prescribing for these patients restricts himself to dose increments of 100 mg, it follows that the majority of the patients will be either undertreated or overtreated. This creates the situation in Fig. 3, where the majority of patients had concentrations below 10 or above 20 μg/ml. In clinical practice many patients with serum concentrations above 20 μg/ml develop overt signs of toxicity and the dose is therefore reduced by 100 mg. This creates the situation in Fig. 1, where the majority of patients had concentrations below 10 μg/ml. If a serum concentration of 10-20 μg/ml is necessary for optimum therapy it is essential to use finer dose adjustments. Increments of 100 mg in daily dose are suitable until the serum concentration reaches 5-10 μg/ml but above that level the suitable dose increment is probably 25 mg; even 50 mg would probably have been large enough to take six of our patients from a concentration below 10 μg/ml to a concentration above 20 μg/ml (Table 1).

Although the phenytoin tolerance test makes it possible to predict a daily maintenance dose for a desired steady state, it is not essential. The physician can probably achieve the same result over a longer period by the process of coarse and fine dose adjustment (Figure 5). Such fine adjustment is only practical for the conscientious patient or the patient whose drug administration is supervised; to forget only two 100 mg doses per week is to reduce the average daily dose by 30 mg.

It has yet to be shown that fine adjustment of dose in 25 mg steps can achieve concentrations of phenytoin consistently within the 10-20 μg/ml range in every patient and that this is accompanied by a more complete suppression of epileptic attacks.

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